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THE ETIOLOGY OF DENGUE
AN ATTEMPT TO PRODUCE THE DISEASE IN THE RHESUS
MONKEY BY THE INOCULATION OF DEFIBRINATED BLOOD *

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It is our purpose somewhat briefly to report experimental work done by us at the United States Marine Hospital, Savannah, Ga., during October and November, 1913, on the attempted transmission of dengue fever to the rhesus monkey by the inoculation of fresh defibrinated blood drawn from cases of the disease, which at that time was epidemic in the city.

Dengue is a disease of special interest to the public health officer on account of its close resemblance epidemiologically and clinically to yellow fever. To the investigator it also offers an inviting field, since the present status of its etiology is such that it apparently offers results of real worth for the expenditure of some time, money and energy.

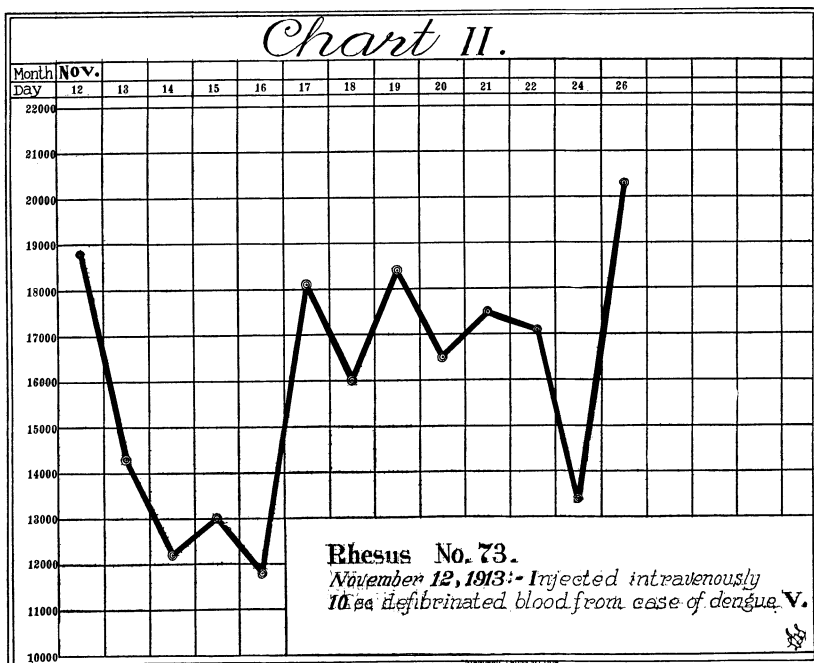
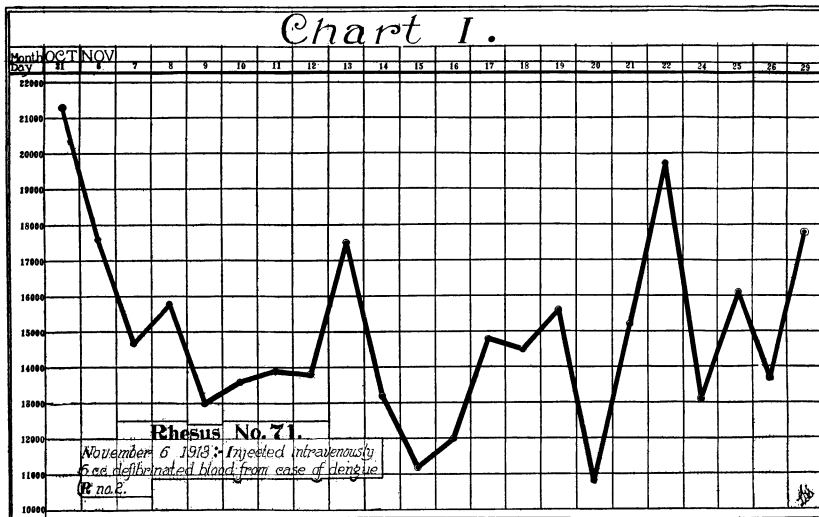
From a review of the subject it would seem safe to assert that dengue is an infectious disease, but is not contagious, that the specific organism is found in the peripheral blood-stream of patients suffering from the disease (at least on the third and fourth days), that the virus is filterable, that no micro-organism of etiological significance has been found in the blood either by staining or by cultural methods, and that the disease is possibly transmitted by the mosquito (*Culex fatigans* and *Stegomyia calopus*). We could find no record in the literature that the disease had been reproduced in animals, and no record of any attempt to reproduce it in the monkey or in the higher apes.

Most, if not all, of our definite knowledge regarding the etiology of dengue rests on the work of Graham¹ and Ashburn and Craig,² especially the latter authors. Their work should, however, be carefully confirmed, especially with regard to mosquito transmission of the disease. Indeed, in its present status, the theory of mosquito transmission of dengue can hardly withstand strict scientific scrutiny.

* Received for publication, June 20, 1914.

1. *Jour. Trop. Med.*, 1903, 6, p. 209.

2. *Philippine Jour. Sc.*, B, 1907, 2, p. 93.



Its confirmation should be undertaken and the matter definitely determined. Our work, however, was exclusively an attempt to reproduce the disease in the monkey by the inoculation of defibrinated blood.

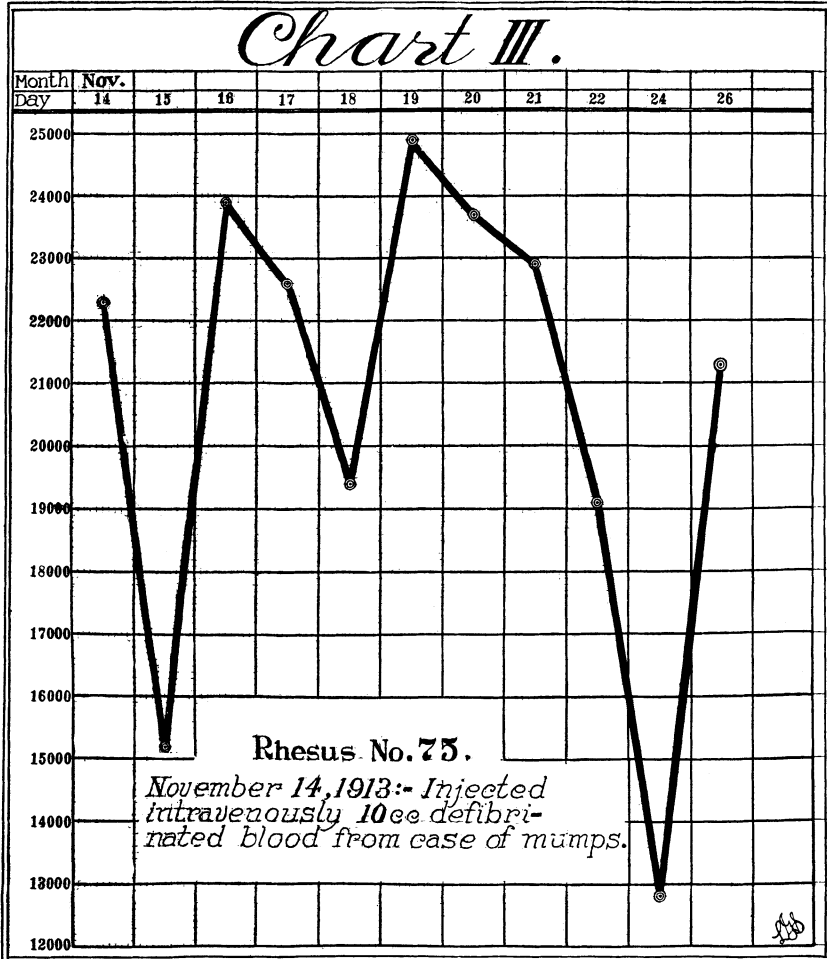
To this end we secured blood from the arm vein of cases of dengue in various stages of the disease, and after defibrination, this was injected intravenously and subcutaneously into monkeys, all as shown in the table given below. The blood was drawn at the residence of the patient with a glass syringe, expelled into a large tube, defibrinated by carefully stirring with a sterile glass rod, brought at once to the laboratory and put in the ice chest until used. For use it was filtered through gauze to get rid of clots. All the monkeys were fresh, healthy, young animals.

TABLE 1
SHOWING CASES OF DENGUE AND ANIMALS INOCULATED

Cases	Quantity Blood Injected	Remarks
E.—4-5th day illness, in eruption	10 c.c. intravenously; 3 c.c. intravenously	Rhesus 9; rhesus 14; Same blood kept 24 hours in ice chest
R.—3-4th day illness	8 c.c. intravenously	Rhesus 10
McA.—2-3d day illness	6 c.c. intravenously	Rhesus 16
S.—4th day illness, in eruption (?)	6.5 c.c. intravenously	Rhesus 23
W.—2d day illness	5 c.c. intravenously; 1 c.c. subcutaneously	Rhesus 25
F.—5th day illness, in eruption, white blood cells 3,000	5 c.c. intravenously; 1 c.c. subcutaneously	Rhesus 24
R2.—3-4th day illness, in eruption; white blood cells 5,900	6 c.c. intravenously	Rhesus 71
V.—3d day illness, in eruption; white blood cells 8,200	10 c.c. intravenously	Rhesus 73

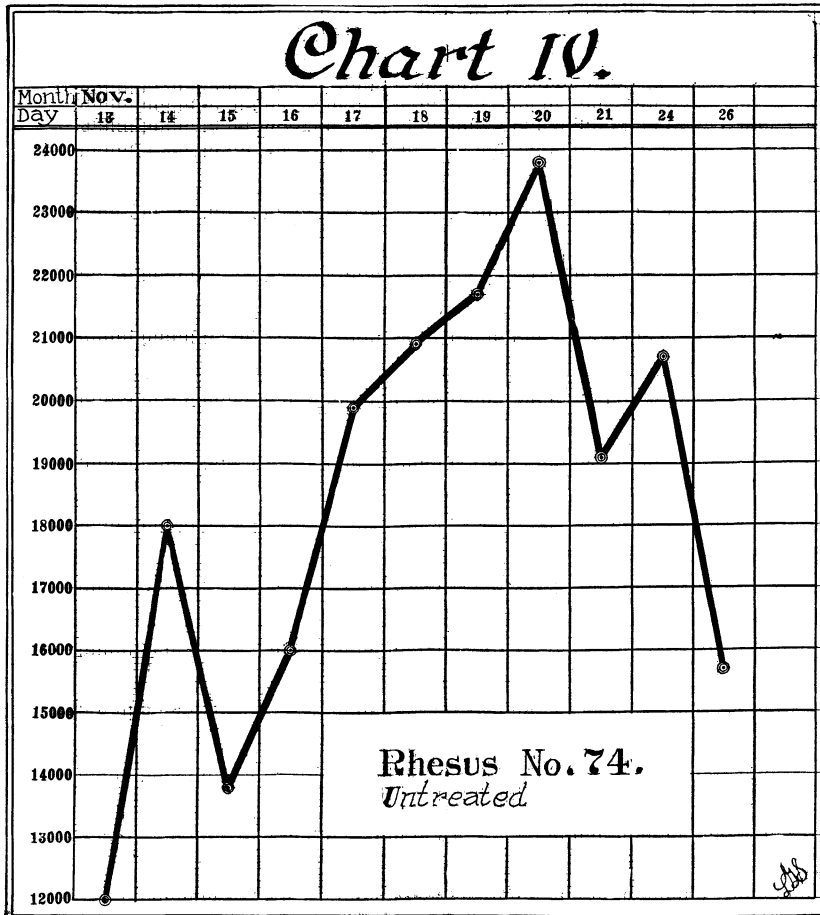
To summarize, it will be seen from the above that we injected intravenously and subcutaneously from 3 to 10 c.c. of defibrinated blood from each of eight cases of dengue into nine rhesus monkeys. The blood was used within two to six hours after withdrawal in all cases but one, where it was kept twenty-four hours in the ice chest. The cases from which the blood was drawn were all carefully selected and in several of them the diagnosis was confirmed by the presence of the characteristic eruption at the time of bleeding. All the animals were carefully examined each day for illness of any kind and for skin eruptions for a period of two weeks. During the same period the temperatures of all were recorded twice daily. They all remained well throughout this period of time and showed no significant deviations of temperature, nor was there any significant skin eruption observed in any of them.

Since leukopenia has been shown to be constant and definite in dengue, it occurred to us that the monkeys might show a similar reaction to the virus, but it was then too late in the epidemic to devote much attention to this. We did, however, make daily leukocyte counts



in Monkeys 71 and 73; and as controls we counted two fresh monkeys, 74 and 75, which latter received intravenously 10 c.c. defibrinated blood drawn from a case of mumps at that time in the hospital. Our counts are shown in the charts, which give the curves of the leukocyte

counts, all of which were made about the same time in the afternoon. The animals were fed at the same hour in the morning. According to Klineberger and Carl,³ the leukocyte count in apparently healthy monkeys may vary as much as 500 per cent. Indeed, their series of



counts show variations from 3,950 to 31,500. They give the average count as 7,470. They used several species of monkeys in making these counts.

Finally, in addition, various quantities of blood from all cases were planted in freshly boiled glucose broth fermentation tubes. Some

3. Die Blutmorphologie Laboratoriums-Tiere, Leipzig, 1912, p. 62.

of these were kept at room temperature and some at 37 C. for several days. Growth appeared in several of the tubes, even after most careful technic, but probably all of the growths might be safely considered as contaminations.

From our work we feel justified in concluding that if dengue is conveyable to the rhesus monkey by intravenous or subcutaneous inoculation of defibrinated blood, these animals do not show the disease by changes in temperature, appearance of skin eruption or any of the ordinary symptoms of illness; further that it is doubtful whether they show any definite and characteristic change in the white blood-cell count, but the results obtained by us are perhaps sufficiently suggestive to invite further effort.